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ABSTRACT

This colloquium book review (occasioned by Andrew Scott's "Pirates of the Cell") contains seven selected readings from popular periodicals and research journals. It is designed to eliminate some of the mental barriers that many have to topics like molecular biology and virology. Included are: (1) "What Is A Virus?" (William D. Elliot); (2) "The Host Cell And Its Metabolic Machinery" (Richard J. Montgomery); (3) "Common Themes in Viral Replication: Lysis and Lysogeny" (Shan Loganathan); (4) "The Body's Response to Viral Invasion" (Robert G. Robertson); (5) "Viral Alteration of Host Cell Function" (Judith N. Peisen); (6) "The Link Between Viruses and Cancer" (Elaine R. Ashby); and (7) "To Fool a Virus--Chemical Mimics" (Robert G. Stenger). The introduction to this compilation is by Judith N. Peisen. Appended is a reading list of books and periodicals. (KR)

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A COLLOQUIUM REVIEW OF

Pirates of the Cell:

The Story of Viruses from Molecule to Microbe

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A COLLOQUIUM REVIEW OF

Pirates of the Cell: The Story of Viruses from Molecule to Microbe

with selected readings from popular periodicals and research journals

presented at
Hagerstown Junior College
Hagerstown, Maryland

Thursday, May 17, 1990, 1:30-3:30 p.m.
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presented by
The Science Division
Hagerstown Junior College

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INTRODUCTION

Judith N. Peisen

Andrew Scott's *Pirates of the Cell* was designed to "introduce viruses to anyone who is interested." The subject is timely. Virology is an exploding science on the leading edge of molecular biology. The explosion is fueled by new technology which permits the culture of viruses within cells grown in the laboratory without risk to a living host and by new funding earmarked for the war on AIDS. The resulting knowledge reaches the scientific community through specialized journals in virology and through general scientific publications like *Science* and *Scientific American*. The general public gets access to all this by newspapers, news magazines, documentary programs, and required science courses. These presentations are often very technical and intimidating.

Scott realizes that many of his potential "interested" readers are intimidated by anything technical. He is a science writer and broadcaster, specializing in biochemistry, molecular biology, and medicine. He uses clear diagrams and familiar examples to bring the reader from the discovery of viruses to the role of viruses in cancer and beyond. His book is organized around the general features that viruses have in common. This approach gives the science-shy laymen a framework to which the complexities of different viruses and their pathologies can be related. Thus, viruses can be a vehicle for driving the laymen into the midst of molecular biology. But how many non-biologists would get past the title and pick up the book? Of those who pick up the book, how many would flip through the pages, see the formulae and diagrams, and think "wow!, finally a book about molecules that I can understand—I can hardly wait to read this"?

This colloquium is designed to eliminate some of the mental barriers that many have to topics like this. We want to empower

INTRODUCTION (continued)

participants in some of the language of biology so that they will be more receptive to books like Scott's and to journal articles like those listed on the program. Viruses are a natural probe to use for this end.

WHAT IS A VIRUS?

William D. Elliott

The name was derived from the Latin meaning slimy liquid, stench, or poison. This name is rather appropriate when one considers how viruses were discovered. In the late 1800s several European scientists including Dimitri Ivanowski independently discovered that the causative agent of tobacco mosaic disease could be transmitted by the filtered extract taken from a diseased plant. The disease caused the plant's leaves to be wrinkled and mottled. Much research was required to determine the true nature of the agent (a virus) that caused this and other plant and animal diseases.

For many years after their discovery viruses were regarded as primitive forms of life, possibly the ancestors of bacteria. This is not surprising in that their discovery occurred during the "golden age" of bacteriology. During this period the causative organisms for many bacterial diseases were discovered; viruses were thought to be simply a primitive form of such organisms.

Teilhard de Chardin, the French priest biologist philosopher, thought viruses were the connecting link between the nonliving and the living world. He poetically described them as having reached a level of complexity that caused them to "glow with life." We now know this view to be incorrect. Beginning with the experiments of Wendell Stanley and others in 1933 the true nature of viruses was elucidated. The following is a brief description of their major findings:

- An extract from a diseased tobacco plant could produce the disease in a healthy plant when the extracted juice was applied to leaf tissue.

WHAT IS A VIRUS? (continued)

- When the extract was boiled before being applied to a healthy plant no disease developed. This demonstrated that the disease causing agent might be a bacterium since most bacteria are destroyed at temperatures above 70 degrees centigrade.
- The extract was then filtered through a porcelain filter with pores smaller than most bacteria (0.5 microns or .000001 meters). This filtration would remove any bacteria present. When this filtrate was rubbed on a healthy plant the disease would manifest itself again.
- A new filtrate was then produced from this diseased plant which also could infect other healthy plants. Thus no dilution seemed to occur ruling out a bacterial toxin as the disease agent. What then was this truly different disease-producing agent which behaved like a poison?
- Further experimental tests indicated that this agent could only reproduce inside the cells of a living tobacco plant; it could not reproduce on artificial media.
- The agent was later precipitated out and crystallized, indicating it was a chemical agent, not a living form! This crystallized form could infect a healthy plant.
- With the development of the electron microscope this chemical agent now known as TMV was found to be rod-shaped and only 0.28 microns in length and 0.015 microns in diameter.

Most biologists now consider viruses to be fragments of cellular genetic material which are usually surrounded by a protein coat. The general structure of viruses shows the genetic material, DNA or RNA, surrounded by a protein coat (capsid). This capsid is composed of protein sub-units and complex ones

WHAT IS A VIRUS? (continued)

can contain several different proteins, carbohydrates, and lipids. In addition the virus particle may possess an outer envelope derived from its host's cell membrane.

These virus particles do not contain mitochondria for energy (ATP) production, or ribosomes for the production of protein which are normally found in eucaryotic cells. Since viruses lack an independent metabolism and cannot reproduce themselves they must insert their genetic material (genome) into a specific host to direct that host cell to produce virus particles. The host cell provides the energy and the organelles necessary for the production of these new viruses. The host cell may then rupture and release the viruses to begin a new cycle.

You may recall that three nucleotides of DNA RNA are required to position a single amino acid of a protein molecule. A protein molecule will usually be comprised of several thousand amino acids. For example the TMV RNA chain contains 6000 nucleotides, thus it has the coding capacity to direct the manufacture of a protein containing 2000 amino acids. This process obviously limits the ultimate smallness of a virus. The virus must contain a genome large enough to code for a minimum of one protein type.

Viruses are extremely host specific. They can recognize specific docking sites on the plasma membrane of a particular cell. When the virus attaches to a specific docking site on the cell membrane it then inserts its genome into the host cell. The viral genetic material may sometimes become incorporated into the cell's DNA. The viral genetic material may also remain separate and take over the host cell machinery for the benefit of the virus.

WHAT IS A VIRUS? (continued)

Some major considerations of viruses are:

- The coming and going of viruses cause viral diseases in some host organisms.
- Viruses can take cellular genes with them and carry these new genes in the next host cell.
- Since they serve as vectors for genes they may have been important in the process of evolution.
- This vector function is used in genetic engineering.

THE HOST CELL AND ITS METABOLIC MACHINERY

Richard J. Montgomery

It is recognized by most all the people that water is the one molecule that is absolutely essential for life. Indeed, it is somewhat tautological, but nevertheless correct, to say that where there is life there is water, and where there is water there is usually life. This statement, true as it is for water, can be applied to other molecules such as enzymes. Enzymes are responsible for controlling the chemical reactions of cells and thus have a paramount role in dictating how a cell will function as well as what it looks like. All of us have enzymes in our cells (about 10,000 total different ones) and as they wear out, new ones are produced so that life will continue. Indeed, if you are lacking a certain enzyme it is entirely possible that this will result in disease and even death. The importance of enzymes to our topic of viruses is simply that viruses do not carry many enzymes around with them and thus must use the enzymes of the host cell in order to multiply.

Before we can understand how a virus usurps the metabolic machinery of the cell to make enzymes, it will be necessary to briefly explore how a cell normally carries out this process. Enzyme production begins in the cell nucleus where the information necessary for this process is stored in a molecule known as deoxyribonucleic acid or DNA. The actual synthesis of enzymes occurs in the cytoplasm of the cell so the information in the DNA must be transferred to the cytoplasm from the nucleus. The process of copying the DNA code is called transcription and occurs when another molecule of nucleic acid, ribonucleic acid (mRNA), is synthesized using the nuclear DNA as a template. As the mRNA (the "m" means messenger) is transcribed, the information for protein synthesis is copied and the mRNA migrates to the cytoplasm. Once in the cytoplasm, the newly synthesized mRNA becomes attached to a small cellular organelle, the ribosome, which serves as a plat-

THE HOST CELL AND ITS METABOLIC MACHINERY (continued)

form or scaffold for making enzymes and other proteins normally needed by the cell. The entire process of enzyme/protein snythesis is timely in that it occurs only when cells need these products, rapid in that enzymes can be produced at the rate of thousands of molecules each second, and elegant in that the whole process is beautifully coordinated by a diverse group of organelles and by a coding system that is remarkable for its simplicity and accuracy.

As has been indicated, viruses are only pieces of nucleic acid surrounded by a protein capsid and in some cases a membranous envelope. Viruses do not have the ribosomes and other machinery to carry out self-replication (as bacteria, plant, and animal cells do). Thus, if a virus is to have a complete life cycle resulting in the production of more virus particles it first must enter the host cell. Entry is complicated and not completely understood by virologists. In spite of this lack of knowledge on the part of virologists, it is still possible to examine how a virus particle enters a host cell and gain some appreciation of the "ingenuity" shown by these naked pieces of nucleic acid.

Entering the Host Cell

The first step is for the virus to find and then become attached to the host cell's outer membrane. Our cell membranes are studded with protein molecules that serve as receptor or recognition sites for a variety of molecules. It is important that cells have these receptor sites since many molecules traveling in our body fluids, if they are to have an effect on a cell's metabolism, must first become attached to the cell membrane.

These circulating molecules recognize the appropriate cell by the protein markers on its surface. Unfortunately evolution has

THE HOST CELL AND ITS METABOLIC MACHINERY (continued)

equipped virus particles with "binding sites" that also allow them to recognize cell receptor sites on the host cell and become attached to them. It is important to realize that not all collisions between a host cell membrane and virus particle will result in attachment. Also, viruses are very selective in their choice of host cell receptors (this is known as host range) and not just any virus will bind to any cell. For example, the polio virus will first bind preferentially to the cells of the digestive tract and then to cells of the nervous system, not to cells in the kidney or skin. Viruses of the common cold infect the cells lining the nasal passage, not cells in the big toe.

Actual entry is achieved in one of three ways. The first is "direct penetration" or translocation of the entire virus across the host cell membrane. In this method of entry the host cell membrane somehow loosens and allows the virus particle to enter. The exact mechanism for this type of entry is unknown. In the second method the virus takes advantage of a process normally used by cells to ingest small clusters of molecules. The process is called pinocytosis and occurs when a virus particle becomes attached and is then engulfed by the cell membrane. The edges of the cell membrane fold up and around the virus until it is completely enclosed. Once inside the cell, this newly formed particle separates from the inside of the cell membrane and floats through the cytoplasm. Before the virus can multiply, it is necessary that enzymes of the virus or host cell uncoat the virus. The last method of entry is found only in those viruses that have their own lipid membrane covering. When a virus particle such as this attaches to a cell, its lipid membrane fuses with the host membrane and the virus particle is released into the cell cytoplasm. A good example of a viral entry mechanism is illustrated by the influenza virus as it enters the cells lining your nose. Initially the virus recognizes the appropriate receptors on the ephithelial cells of your nasal passage. Once attached, the virus

THE HOST CELL AND ITS METABOLIC MACHINERY (continued)

is engulfed by pinocytosis. Inside the cytoplasm the double membraned virus fuses with a cellular lysosome. Here the viral coatings are stripped and the virus is eventually released into the cytoplasm as a naked piece of nucleic acid. Once here it takes over cell enzymes and ribosomes, starts to multiply, and your misery begins.

COMMON THEMES IN VIRAL REPLICATION: LYSIS AND LYSOGENY

Shan Loganathan

Viruses are obligate intracellular parasites and need living tissue for their survival and reproduction. Plants, animals, insects, bacteria, and many other living things serve as hosts for various types of viruses.

Reproduction of viruses (usually called replication) is a complex process for which the mechanism was worked out in the 1950s. A knowledge of viral replication is essential for understanding the disease process caused by viruses. For example, it has been experimentally determined that a nerve cell infected with one polio virus disintegrates in six hours producing about 10,000 new polio viruses. Each new virus attacks a new nerve cell which disintegrates after another six hours producing another 10,000 new viruses and thus destroying the nervous system. One can now understand how the process of paralysis gets started in a polio patient.

The replication of a bacterial virus (called a bacteriophage) consists of the following stages: attachment, genome penetration, RNA synthesis (transcription), protein synthesis, genome replication, assembly of new virions, and release. First, the phage attaches itself to the surface receptors of the bacterium by its tail fibers. The viral genome (RNA OR DNA) is then injected into the bacterial cell with the protein coat being left outside. Once inside the bacterial cell, the viral DNA directs the synthesis of viral mRNA which is used to make viral proteins, and viral enzymes which catalyze the production of more copies of the viral genome. The various proteins and DNA thus formed assemble themselves into viral components such as the head, tail, and tail fibers. In about 30 minutes, the bacterial cell breaks down (lysis) releasing thousands of new viral particles.

COMMON THEMES IN VIRAL REPLICATION: (continued)

Not all viruses cause the lysis of host cells. The so-called temperate viruses, once inside the host bacterial cell, become integrated in the genome of the bacterium which does not die. This type of viral cycle is called lysogeny. Actually, the bacterium becomes genetically altered and goes on dividing in the normal manner. Each time the bacteria reproduces itself, it makes another copy of the integrated viral genome also. Sometimes the viral DNA becomes separated from the bacterial genome under the influence of ultraviolet light or chemical agents. (This process is called induction.)

Animal viruses replicate in the same way as these bacteriophages with a few variations. For example, since animal cells lack a cell wall, the animal viruses attach to the plasma membrane of host cells and gain entrance by fusing their envelopes with the plasma membrane or by pinocytosis (a process of engulfing by the cell). In most cases, however, the entire virus enters the animal cell and the virus uncoating takes place later. There is also a great variation in the way that animal viruses direct the synthesis of their genome due to their complex genetic makeup (RNA, DNA, single stranded, double stranded, etc.). The non-enveloped animal viruses finally escape from the host cell during lysis while the enveloped animal viruses escape when they pinch off from the plasma membrane.

THE BODY'S RESPONSE TO VIRAL INVASION

Robert G. Robertson

In the human, like other multicellular organisms, the cells which a virus invades are a small part of the whole. The effect on the whole organisms depends on the role of the susceptible cells. It is of little advantage for viruses to be so effective at commandeering host cells that they kill the whole organism since that would eliminate their resources for survival and replication. Therefore, viral hosts have evolved effective means of coexisting with these molecular pirates. Specific populations of cells have evolved to present an organized defense against any foreign cells and molecules, including viruses. These cells make up the immune system of an organism. Defense against viruses is more complicated than defense against bacteria and other microorganisms because viruses are usually inside host cells and "concealed."

The human immune system has two types of defense mechanisms against viral infections: the non-specific mechanisms which work against ANY virus (or other microorganisms) and the specific immune responses which work only against a particular virus. For example, the measles virus, the HIV virus, and the polio virus must all gain access to their target cells (with the appropriate receptor), by getting through specialized cells on the surface of the body called keratinized skin on the outside or mucous membrane on the inner surfaces. A break in this barrier may allow viruses access to cells with the necessary receptors. The measles virus enters through the respiratory route, the HIV virus must enter directly into the blood stream in body fluids, and the polio virus enters through the intestinal route. If the virus is successful in finding a target cell, the non-specific mechanisms to eliminate the infected host cell include phagocytosis and the inflammatory response. Phagocytic cells known as neutrophils, monocytes macrophages, and NK (natural killer) cells roam

THE BODY'S RESPONSE TO VIRAL INVASION (continued)

the body searching for viruses in the blood and cells. They are all specialized forms of white blood cells which can engulf and digest virally infected cells in various ways.

Infected cells produce small proteins called interferons. These molecules help neighboring cells resist invasion by new viruses. They are active against many different viruses (which is why they are part of the non-specific response) but they are host-specific. Thus, interferons produced in other animals have no antiviral action in humans.

The infected cells in a region also trigger the inflammatory response which causes blood vessels in the area to dilate which increases the blood flow. This makes the region red and swollen. As the swelling (called edema) increases it often causes the pain characteristic of inflammation.

Finally, there is fever. Macrophages (one of the phagocytic cells described above) produce molecules known as pyrogens which are released into the blood stream and circulate all over the body, including the hypothalmus of the brain. This is the thermostat of the body and the pyrogens cause the thermostat to be reset at a higher temperature. This causes fever and the host begins to feel really sick because the host cell enzymes do not function as well at high temperatures. This will interfere with the virus because the virus is dependent on host cell functions. At this point the person with this infection is definitely feeling sick, not because the virus has done a lot of damage yet, but because of the non-specific defenses against the virus which interfere with cell functions.

Now, the body's specific immune response, mediated by a group of blood cells called lymphocytes, begins to develop. Lymphocytes are able to recognize these invaders as "non-

THE BODY'S RESPONSE TO VIRAL INVASION (continued)

self" entities made up of foreign proteins referred to as "antigens." Landmark experiments by Von Behring and Kitasato in 1890 revealed the basis of the specific immune response. They showed that animals surviving a serious infection had developed protective factors in their blood that protected them from future attacks of the same disease-causing organism (called a pathogen). Furthermore, they showed that serum taken from these infected animals and injected into healthy animals protected the healthy animals from this infection also. Their investigation illustrated three important aspects of this specific immune response:

1. It is antigen-specific.
2. It is systemic—not just limited to the initial infection site.
3. It has memory and will protect the animal from future attacks on the same pathogen.

Later studies showed that these protective factors in the blood serum were highly reactive proteins. They were subsequently named "antibodies." Thus, a virus is made of many proteins called *antigens* which are foreign to the body and cause the specific immune response to produce *antibodies* to these specific viral antigens. Eventually, it was shown that injected serum containing antibodies did NOT serve as complete protection against certain infections, particularly viral infections. It was shown that lymphocytes, a specialized type of white blood cell, extracted from a donor, provide the specific immune response. As the pieces of the puzzle began to fall into place, two separate but overlapping forms of specific immunity were recognized. Both types involve the activity of lymphocytes, but only one type involves antibodies. These two types of specific immune response are called the humoral response (antibodies) and the cell-mediated response (CMI).

THE BODY'S RESPONSE TO VIRAL INVASION (continued)

To understand the two types of specific immunity, we must look at the development of lymphocytes. All lymphocytes initially arise in the bone marrow. Some of them migrate to the thymus gland and mature to become T-lymphocytes or simply T-cells. T-cells are responsible for CMI. Other lymphocytes mature and develop their antigen-specific immunocompetence elsewhere and are known as B-lymphocytes or simply B-cells. These cells are behind the antibody response.

When an invading virus first encounters a lymphocyte it is probably in the spleen or a lymph node where both T-cells and B-cells are stored. If the lymphocyte is a B-cell, the challenging antigen elicits the humoral response and the B-cell will begin to produce antibodies that clump with the viral antigens and attempt to remove it from the blood. The antibodies will be *ineffective* if the virus has already entered a host cell where it can "hide" from the antibodies. Antibody protection works best against bacteria and other cellular microorganisms because the antibodies can bind to the foreign cell surface and identify the cell for molecules that will actually pierce the cell membrane and cause its contents to leak out. Since viruses are not cells, this will not work.

Therefore, CMI, the T-cell mediated response is required to completely clear a viral infection. This process is much more complex than the B-cell response. There are four different populations of T-cells:

1. Cytoxic T-cells
2. Delayed hypersensitivity T-cells
3. Helper T-cells
4. Suppressor T-cells

THE BODY'S RESPONSE TO VIRAL INVASION (continued)

When an immature T-cell "sees" an antigen in combination with a "self" protein on the surface of a body cell at the same time it triggers dramatic growth and multiplication (referred to as cloning) of the T-cell, the body cell which appears to play the major role in presenting the double signal to the immature T-cells is the macrophage which was on the frontlines of the non-specific defenses described earlier. The resulting family of identical T-cells which are all specific for the same antigen, is called a clone. Shortly thereafter, these T-cell clones begin to differentiate into the four different kinds of T-cells. Helper T-cells produce molecules known as lymphokines which communicate with the cytotoxic T-cells and facilitate their activation to eliminate an infected body cell. Suppressor T-cells mature, develop later, and turn off the cytotoxic T-cells so that the immune response will stop when the virus is under control. If the suppressor T-cells do not function correctly, the immune response continues even after the virus is cleared and may damage the host itself.This is one possible mechanism to explain autoimmune diseases in which the immune response is turned on inappropriately as in rheumatoid arthritis.

VIRAL ALTERATION OF HOST CELL FUNCTION

Judith N. Peisen

When the cell which a virus invades is part of a large multicellular organism like the human, there are many patterns of disease that can result. These patterns can be divided into four broad categories of viral infections.

1. Acute infections result when the virus replicates effectively inside the host cell and results in cell death. The cell dies because it cannot make its own proteins and enzymes anymore or because its membrane is disturbed so much that its contents leak out. The symptoms of this type of infection will depend on what kind of cells are killed and the immune response. Acute viral infections are cleared by all parts of the immune system: immediate and non-specific, humoral immunity (antibodies), and CMI (T-Cell Mediated Immunity). As mentioned in a previous presentation, without a competent CMI response, viral infections *cannot* be cleared.
2. Latent infections result when an acute infection is NOT cleared completely by the immune system. Instead, the virus enters a quiescent phase, there is no detectable virus and no symptoms. Usually the virus has integrated into the host cell DNA and the immune system will not attack it. This strategy is normal for some viruses like the Herpes virus and abnormal for other viruses like measles. Latent viruses can become reactivated and a flare up will cause reoccurrence of disease symptoms.
3. A slow virus infection is not the same as a latent infection because there is no initial acute infection. Instead, there is a slow increase in virus levels and a slow production of viruses. This has to happen in cells which are safe from immune attack because the virus is not cleared

VIRAL ALTERATION OF HOST CELL FUNCTION (continued)

as it would be if there were an effective immune response. An example of this is a disease called Kuru in which the virus infects brain cells and causes slowly progressing brain damage. The T-cell immune response is not effective in nerve cells because the nerve cells lack the MHC marker necessary to activate cytotoxic T-cells. Thus, the virus is able to survive by hiding inside nerve cells that are not recognized by cytotoxic T-cells. This virus is spread when the brains of infected victims are prepared for consumption by surviving relatives in a culture which encourages this as a sign of respect for the dead.

4. The last type of viral infection is the persistent infection in which there is no cell death. Virus levels are high in persistent infections, but the immune response is inadequate to clear the virus. The host cells are not killed because the replicating virus does not interfere with vital functions of the cell. The cells look perfectly normal. However, the cell may have a "luxury" function which is important for the survival of all the other cells in the body. Nerve cells must be able to produce neurotransmitters, endocrine gland cells must be able to produce hormones, and immune cells must be able to produce lymphokines and other molecular signals.

It is easiest to consider persistent infections by looking at several examples. Much of the research on these infections has been done with a special strain of laboratory mice in which the LCMV virus replicates preferentially in pituitary cells. The pituitary cells are not killed by the infection even though much viral replication occurs. However, the amount of growth hormone produced by these cells decreases by 50% and the mice have retarded growth and hypoglycemia (low blood sugar).

VIRAL ALTERATION OF HOST CELL FUNCTION (continued)

There is no immune response to this infection and the molecular mechanism which allows the virus to persist without causing an immune response is unknown.

A persistent virus can also invade the beta cells of the pancreas. The infected islet cells appear normal and there is no inflammation. However, insulin production is impaired and diabetes results.

A fetal rubella (German measles) infection can become persistent also. In this case, the mother is infected with the virus during her pregnancy and her immune response is slow because this is a very simple, non-threatening virus with low pathology to an adult. The slow immune response of the mother allows the virus to spread to the fetus. However, the death of cells in a fetus is much more serious because each cell is the precursor to many cells. The T-cell mediated immune response in a baby does not develop until about six months after birth which means that the virus will *not* be cleared in the fetus. Since it is able to replicate for much longer than it replicates in an adult, there is an increased probability that it can mutate into a form that will remain persistent even after the T-cell immune response develops. Many children with a history of fetal rubella infection have retarded growth and diabetes that may be the result of a persistent rubella infection.

There are many other examples: measles, chicken pox, and mumps are all caused by viruses that can be persistent in the central nervous system (where the T-cell immune response is not effective). Cardiomyopathy has been linked to persistent viruses in heart muscle. Autoimmune diseases such as rheumatoid arthritis have been linked to persistent infections in suppressor T-cells.

VIRAL ALTERATION OF HOST CELL FUNCTION (continued)

The mechanism for the establishment of a persistent infection requires an incompetent cell-mediated immune (CMI) response. Remember that the normal CMI requires that a cytotoxic T-lymphocyte recognizes an infected cell by two markers on its surface: the MHC-1 marker and the viral antigen marker. This does not work in a newborn mouse so the seed virus replicates without being cleared by cytotoxic T-cells. The repeated replication provides increased opportunities for viral mutations. Any mutation which will interfere with the production of cytotoxic T-cells that recognize the infected cell markers will tend to survive which would lead to a virus that cannot be cleared, i.e., a persistent infection.

These mutant viruses which are able to resist clearing by CMI can be spread to new hosts where they continue to resist clearing. Thus, a child with a persistent rubella infection that was acquired prenatally, can spread the infection to an older child with normal CMI because the mutated virus has some way of evading a normal immune response.

There are many disorders that may be involved with persistent viral infections. Viruses used to be blamed for diseases only if there was a specific type of pathology and cell destruction found. Now, viruses are suspected if there is a disorder of the specialized functions of nerve cells, endocrine cells, and immune cells. The number of such disorders is very large.

THE LINK BETWEEN VIRUSES AND CANCER

Elaine R. Ashby

Cancer is one of man's most dreaded diseases. Three out of every ten Americans will eventually get cancer and one of every five will die from it. An estimate of total cost attributable to cancer (including medical bills and lost wages) is greater than 70 billion dollars a year.

"Cancer is a growth disease of cells in which the controls that normally restrict proliferation do not operate" (Raven and Johnson). Normal cellular growth is regulated by enzymes and regulatory proteins coded in the DNA. This DNA is organized into genes which are inherited in two copies, one from each parent. If one copy lacks the code for molecules which regulate cell growth and replication, the other copy may mask that absence. If both copies of a regulatory gene are damaged, regulation will not be normal. The genes may be altered by a variety of forces including ultraviolet radiation, chemical carcinogens, and cancer viruses. Any kind of mistake in the replication of DNA no matter what the cause may alter gene regulation. If the regulatory genes of a cell become altered, that cell begins to grow in an uncontrolled and invasive way, resulting in cancer. A single cancer cell can be isolated, then transplanted into a healthy animal. Because its genetic message is one of uncontrolled growth, that one cell will grow in an uncontrolled manner until it forms a full-sized cancer.

Viruses have been blamed for causing genetic damage which induces 20% of world cancers. Hepatitis B virus has been linked to liver cancer known as hepatocarcinoma. Epstein Barr virus has been linked to lymphomas and nasopharyngeal cancer. Human papilloma virus has been linked to cervical and genital cancers and retinoblastoma.

THE LINK BETWEEN VIRUSES AND CANCER (continued)

Virologists use several criteria to establish the link between viruses and human cancers:

1. The incidence of some types of cancer are correlated with the incidence of infection by a specific virus. For example, the chance of getting liver cancer if you have had hepatitis is about 100 times greater than for those who have not had the disease. Since infection by viruses is not always obvious, it is sometimes established by the presence of antibodies directed against a particular virus. The antibodies then establish the link between the virus and the cancer.

2. The onset of many cancers is often preceded by infection by a specific virus.

3. Viruses or some part of a virus (the viral genetic material) can often be found in the cancer cells. Virus purified from these cells will then cause cancer in laboratory animals or cause human cell cultures to transform into cancer-like cells.

4. Finally, vaccinations against the virus should decrease the incidence of the cancer. Several countries in Asia, where there are both high rates of Hepatitis B and liver cancer, have begun infant vaccination programs. It will take many years until there are clear results from these programs, but the chances of successfully reducing liver cancer by vaccination in this case appear to be promising.

Since cancer is the result of healthy cells that begin growing in an uncontrolled manner, viruses with a causative role in cancer must act in a lysogenic rather than a lytic manner. If the viruses go into a cell, produce more viruses, then burst the

THE LINK BETWEEN VIRUSES AND CANCER (continued)

cell (lysis) there would be no transformed cells to grow into tumors. Lysogenic viruses, as described in a previous presentation, cause cancer by several different mechanisms. It is easier to look at the mechanisms of DNA viruses and retroviruses separately.

When DNA viruses enter their host cell, their DNA can become integrated into the cellular DNA. Then the host cell may begin to produce proteins coded from the viral DNA which transforms the normal cell into a cancer cell. An example in humans is the case of retinoblastoma, a tumor of the eye. Researchers have found that retinoblastoma is caused by the absence or inactivation of the host cell retinoblastoma gene which is believed to have a role in inhibiting cell growth. Papilloma virus includes two genes whose protein products form stable complexes with the retinoblastoma protein, thereby inactivating it and allow the host cells to grow without its inhibitory effects.

Retroviruses do not have DNA. Instead, they contain RNA which they copy into DNA after the virus enters its host cell. Retroviruses, like the HIV virus which causes AIDS, are the only RNA viruses that can cause cancer because the DNA which they make can integrate into the host cell DNA which transforms the host cell genome in several ways which may result in cancer. Sometimes the retroviruses copy cancer-causing genes (oncogenes) that are a normal part of the cell's genome are suppressed by other genes. The virus incorporates this oncogene into its genome and when that virus infects future cells the oncogene may not be suppressed properly and the harmful oncogene will be expressed. The retrovirus may also facilitate the reshuffling of normal genes into positions which handicaps the suppressor gene's ability to prevent transformation. Finally, the RNA virus may act in a

THE LINK BETWEEN VIRUSES AND CANCER (continued)

manner similar to DNA viruses by coding for proteins that cause cellular transformation.

It appears that viruses do play a role in human cancers but they are not the only culprits in this disease. This is supported by several pieces of evidence: there is often a long time between initial viral infection and eventual development of cancer; viruses are common but not all people who are infected with a viruses will eventually get cancer, and not all cancers have been linked to viruses.

Viral research can contribute to our understanding of cancer. Thus research and vaccination programs may help to reduce the incidence of cancer in the future.

TO FOOL A VIRUS - CHEMICAL MIMICS

Robert G. Stenger

A Swiss alchemist and physician, Paracelsus, in the early 1500s began to depend upon the use of a variety of chemical agents in the treatment of disease. It was nothing new to use chemical agents for such a purpose, but what was new was that the substances employed were not of plant or botanical origin as was formerly the case. He referred to such uses of chemicals in the treatment of disease as iatrochemistry. By the 1600s a Dutch physician by name of Sylvius had greatly systematized the body of such knowledge.

A more generally recognized term is chemotherapy which can be defined as the use of certain chemical agents (or drugs) that specifically kill infectious organisms without harming the patient - a classic case of winning the battle but losing the war. Before the turn of the century, only a very few chemical agents were in use and several of them were (and had been for many years) from the botanical world. The New World gave the bark of the cinchona tree as the source of treatment for malaria - really one of many gifts the Amerindians have presented to the world. But there were few others against the onslaughts of disease.

Paul Ehrlich discovered an agent he called "Salvarsan" in 1909 that proved very useful against the organism that caused syphilis. It was also for a time known as "606" because Salvarsan was the result of the 606th experimental series.

Up until the period immediately prior to the outbreak of World War II, quite a number of chemicals were checked out as possible "bullets" against diseases. Success was limited and spotty at best, but in 1936 a French researcher found that what is known as a sulfa drug was most effective against streptococci. The basic chemical matrix proved to be sulfanilimide

TO FOOL A VIRUS - CHEMICAL MIMICS (continued)

which can be altered in almost countless ways into other specific chemical bullets. In 1940 it was determined that p-aminobenzoic acid is needed by bacteria to synthesize folic acid, another substance important in the organism's continued development. The new chemicals, the sulfanilamides, are mimics of the p-aminobenzoic acid in that they occupy a vital site in a needed bacterial enzyme, and thereby inactivate it - lock and key if you will. It is hard to say how many people would have died of pneumonia had it not been for the sulfa drugs - on the battlefield, as well as at home.

But these drugs for a variety of reasons are totally ineffective against the viruses. However, the concept of a mimic is still valid, but using different agents.

As DNA and RNA became better characterized after their initial discovery, it was thought that altered chemical agents called nucleosides could prove of use in combatting certain cancers, for instance, 5-fluorouracil, a slightly different form of the naturally-occurring pyrimidine - uracil. It is a short, but significant step to see that perhaps such modified chemicals might short-circuit the development of a virus if they could take the place of a needed naturally-occurring nucleoside.

Before a consideration of how a chemical mimic, or analogue could function, it is important to examine the structures of still simpler chemicals, e.g., ribose deoxyribose (the two sugars found in RNA and DNA), and guanine, one of the nitrogeneous bases found in nucleic acids as well. The next step is to see how guanine is combined with a deoxyribose to form what is called a nucleoside - and one specifically named deoxyguanosine. In a virus, normally occurring nucleosides combine with a particular counterpart and the virus continues its development.

TO FOOL A VIRUS - CHEMICAL MIMICS (continued)

But suppose an altered nucleoside - perhaps missing a critical portion of the overall structure - is prepared and incorporated into the tissues in which the virus is present. The virus will continue its attempt at finishing its growth only now to have within itself a built-in roadblock to additional development. With the mimic missing a vital subsection of the natural nucleoside firmly in place in the growing virus, the growth process is halted.

A chemical mimic that seems to operate in the manner already described is acyclovir. If one examines it structural formula, it can be seen that a major portion of the deoxribose substructure is totally missing, and any viral DNA that has incorporated the mimic will cease to develop further.

Problems exist even if the picture presented appears encouraging. The relief may be of symptoms and not really be a long-term cure. The drugs - the chemical mimics - may be very toxic to the patient, and only a short-term course may be advised or even possible. Then the virus may mutate and render the drug totally ineffective. Protection against future infection may not be instilled. Viruses vary different, obviously, one from another. Just where, in the cycle of viral replication, can a chemical mimic be inserted? And what is the mimic itself? Development costs are enormous and the time needed to bring a new drug into general usage is not an overnight consideration.

But one point is clear: viruses grow. To develop, they must utilize a variety of chemical precursors. So, as has been seen, they interrupt a necessary link in the cycle of replication, and some measure of control is in hand.

TO FOOL A VIRUS - CHEMICAL MIMICS (continued)

It is of interest to know that literally thousands of plant tissues (flowers, roots, stems, etc.) are screened every year in an ongoing search for chemical substances (naturally occurring) that may prove advantageous in the control if not cure of disease.

Ironic as it may be, the rainforests of the planet as they continually shrink under the onslaughts of development for whatever the reason, may be taking with them as they recede into oblivion those very substances that could well offer a solution to many scourges - old and new.

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